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Value of pulmonary artery pressure in predicting in-hospital death and one-year mortality after valve replacement surgery in middle and aged patients with rheumatic mitral disease: an observational study

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Abstract

Objectives: To investigate the role of pulmonary artery pressure (PAP) in predicting in-hospital death after valve replacement surgery in middle and aged patients with rheumatic mitral disease.

Design: A prospective observational study.

Setting: Guangdong General Hospital in China

Participants:1639 middle and aged patients diagnosed with rheumatic mitral disease undergoing valve replacement surgery and receiving coronary angiography and transthoracic echocardiography before operation were enrolled.

Interventions: All participants underwent valve replacement surgery and received coronary angiography before operation.

Primary and secondary outcome measures: In-hospital death and one-year mortality after operation.

Methods: Included patients were divided into four groups based on the preoperative PAP obtained by echocardiogram: group A (PAP≤30mmHg); group B (30mmHg<PAP≤50mmHg), group C (50mmHg<PAP≤70mmHg) and group D (PAP>70mmHg). The relationship between PAP and in-hospital death and cumulative rate of one-year mortality were evaluated.

Results: In-hospital mortality rate increased gradually but significantly as PAP level increased, with 1.9% in group A (n=268), 2.3% in group B (n=771), 4.7% in group C (n=384), and 10.2% in group D (n=216) (P<0.001). Multivariate analysis showed that PAP>70mmHg was an independent predictor of in-hospital death (OR=2.93, 95%CI:

1.61-5.32, P<0.001). PAP>52.5mmHg had a sensitivity of 60.3% and specificity of 67.7% in predicting in-hospital death (AUC=0.672, 95%CI: 0.602-0.743, P<0.001). Kaplan-Meier analysis showed that patients with PAP >52.5mmHg had higher one-year mortality after operation than those without (Log-Rank=21.51, p<0.001).

Conclusions: PAP could serve as a predictor of postoperative in-hospital and one-year mortality after valve replacement surgery in middle and aged patient with rheumatic mitral disease.

Key words: Pulmonary artery pressure, rheumatic mitral disease, valve replacement surgery, death

Strengths and limitations of this study

1.3.8% middle and aged patients receiving mitral valve replacement suffered death during or shortly after surgery

2.PAP could serve as a predictor of postoperative in-hospital mortality after valve replacement surgery in middle and aged patient with rheumatic mitral disease.

3.PAP>52.5mmHg had a sensitivity of 60.3% and specificity of 67.7% in predicting in-hospital death

4.PAP >52.5mmHg had higher one-year mortality after operation than those without.

5.Since the reproducibility and reliability of echocardiography in calculating PAP are lower than right-side heart catheterization, clear correlation between PAP level and post-surgery mortality was unknown.

1.Introduction

Rheumatic heart disease (RHD) caused by rheumatic fever has been uncommon in developed countries, but it still remains as a major health problem in developing countries. [1,2] Approximately 50% of RHD affects mitral valve, resulting in mitral stenosis, mitral regurgitation, or both. [3] Valve replacement surgery is an important treatment for rheumatic mitral disease. [4] However, according to the meta-analysis conducted by Guida et al. [5], 2.95% (4293/145592) patients undergoing cardiac surgery including valve replacement suffered postoperative mortality. Therefore, identifying the high risk factor(s) for poor outcomes remains urgent and important.

Pulmonary hypertension (PH) is a common complication of rheumatic mitral disease which is correlated with poor outcome in patients undergoing heart surgery, particularly those middle and aged patients. [6] Pulmonary artery pressure (PAP) can be easily measured using Doppler echocardiography, which is currently considered the best screening method for PH. [7] However, whether the PAP could serve as a suitable readout or predictor for poor outcome particularly high mortality in patients with rheumatic mitral disease is not clearly and the cut-off value for PAP as a predictor has not been defined. The present study is designed to determine whether PAP could be a valuable parameter in predicting in-hospital death or cumulative rate of one-year mortality after surgery in middle and aged patients with rheumatic mitral disease.

2.Patients and Methods

2.1. Patients

In this prospective study cohort, we enrolled the middle and aged patients diagnosed as rheumatic mitral disease from Guangdong General Hospital, Guangzhou, China between March, 2009 and July, 2013. RHD was diagnosed according to previous acute rheumatic fever and/or symptom of precordial abnormalities, the presence of heart murmur, and the valve abnormality on echocardiography. [8] All patients received mitral valve replacement surgery in this study. PAP levels were measured using transthoracic echocardiography and coronary angiography was performed to exclude coronary heart disease in all patients. The exclusion criteria were (I) patients with known primary PH or pericardial disease, (II) patients presenting with pulmonary vessel disease and chronic obstructive pulmonary disease, (III) patients with previous valve replacement surgery and (IV) patients did not have echocardiographic examination before surgery.

1639 patients were divided into four groups based on the preoperative PAP on echocardiography. Patients in group A had $PAP \leq 30mmHg$ (n=268); patients in group B had $30mmHg < PAP \leq 50mmHg$ (n=771); patients in group C had $50mmHg < PAP \leq 70mmHg$ (n=384) and patients in group D had $PAP > 70mmHg$ (n=216). The cut-off values were decided according to clinical guidelines (5,6). This study was approved by the Ethics Committee of the hospital (GDREC2014016H R1) and written informed consents were obtained from all enrolled participants.

2.2. Echocardiography

M-mode, 2-dimensional, and Doppler tissue imaging were performed according to guidelines of the American Society of Echocardiography [9] before valve replacement surgery. Left ventricular end-diastolic and Right ventricular diameter were obtained in the parasternal long-axis view by using M-mode images. Left ventricular ejection fraction (LVEF) was evaluated using the biplane Simpson’s method. Mitral and tricuspid regurgitation were measured based on the jet area within the left or right atrium, respectively. Pulmonary artery pressure (PSP) was estimated by Doppler echocardiography with calculating the right ventricular to right atrial pressure gradient during systole, approximated by the modified Bernoulli equation as 4v2, where v is the velocity of the tricuspid regurgitation jet in m/s. [10] Although the agreement between echocardiographic estimates of PSP and invasively measured values on right-side heart catheterization is suboptimal, [11] especially among patients with lung disease, [12] echocardiography is a more convenient and practical approach than right-side heart catheterization. On the other hand, both echocardiography and right-side heart catheterization have been reported to be sufficient methodology PH screening. [13]

2.3. Definitions and endpoints

Coronary artery disease was defined as main coronary stenosis≥50 according to coronary angiography. The primary endpoint of this study was death from any cause except suicide during hospitalization. One-year mortality after operation was considered as secondary endpoint.

2.4. Statistical analysis

Continuous variables were described as mean± standard deviation (SD) and difference among groups was compared by analysis of variance (ANOVA) and post-hoc analysis was further performed to detect the difference between two particular groups. Abnormally distributed data was shown as median (first and third quartiles) and difference was analyzed by non-parametric Mann-Whitney U test. Categorical variables were shown in the format of numbers (percentages), and the comparison of the groups was done by $\chi 2$ test. Multiple logistic regression analysis was performed to discovered the risk factors. Receive operative characteristic (ROC) was presented to evaluate the predictive value of PAP for in-hospital death. All the statistical analyses were carried out using SPSS 11.0 software program and $P < 0.05$ was considered statistically significant.

3.Results

3.1. Baseline clinical characteristics of the cohort

1749 middle and aged patients with rheumatic mitral valve disease underwent valve replacement surgery was originally enrolled in this study, among which 19 patients had a past medical history of valve replacement surgery. Preoperative echocardiography data was missing in 90 patients and 1 patient committed suicide during hospitalization, resulting in a final of 1639 patients being recruited in this study. 512 subjects were males and the remaining 1127 subjects were females with an average age of 57±6 years.

Other clinical characteristics of this population was summarized in Table 1. In brief, patients in other groups had higher incident of atrial fibrillation than patients in group A (p=0.006 of χ^2 test), possibly due to their high PAP and potentially changed left atrium structure. There were significant differences in the proportion of NYHA>II and right ventricle (RV) diameter among four groups, with patients in group D who had highest PAP having the largest percentage of subjects of NYHA>II and biggest RV diameter (Table 1). Lower hemoglobin was observed in group C and D compared with group A (ANOVA P<0.001, and post-hoc test P<0.05 vs group A). In addition, lower LVEDD index and mitral regurgitation volume were presented in group D (ANOVA P<0.001, and post-hoc test P<0.05 vs group A). Besides, patients in group C had a significantly lower LVEF compared with group A (p<0.05). Increasing PAP level was associated with higher tricuspid regurgitation volume (ANOVA P<0.001). 63 patients died during hospitalization with 5(1.9%) in group A, 18 (2.3%) in group B, 18 (4.7%) in group C and 22 (10.2%) in group D (p<0.001 of χ^2 test). No significant differences in the clinical data was observed among groups.

Among all these 1639 patients, 1459 subject (89.0%) completed the one-year follow-up after operation, during which time 75 patients died including 7(3.0%) in group A, 23 (3.3%) in group B, 20 (5.9%) in group C and 25(13.2%) in group D (p<0.001).

3.2. Correlation analysis between PAP levels and other parameters

Among all patients, PAP levels had positive correlation with RV diameter (r=0.270, p<0.001) and tricuspid regurgitation volume (r=0.507, p<0.001), and negative correlations with eGFR (r=−0.074 p=0.003), LVEDD index (r=−0.204, p<0.001) and hemoglobin concentrations (r=−0.141, p<0.001).

3.3. Role of PAP for in-hospital mortality

The univariate analyses for mortality showed that age, diabetes mellitus, anemia, lower eGFR, LVEF<50%, larger RV diameter, TR volume, previously received CABG and higher PAP were associated with increased in-hospital mortality (Table 2).Then we put these variables into multiple logistic regression analysis for adjustment of potential biased factor, we found that PAP>70mmHg (OR=2.93, 95%CI,1.61-5.32, P<0.001) remained an independent predictor of in-hospital death, after adjusting age, diabetes mellitus and previously received CABG. Of note, age (OR=1.07, 95%CI, 1.02,1.12, P=0.006), diabetes mellitus (OR=2.50, 95%CI, 1.16-5.38, P=0.019), LVEF<50% (OR=2.09, 95%CI, 1.05-4.15, P=0.036), TR volume (OR=1.05, 95%CI, 1.01-1.09, P=0.021) and received CABG (OR=2.96, 95%CI, 1.26-6.93, P=0.012) were also independent risk factors for in-hospital death (Table 2).

In addition, we performed a ROC curve to determine the predictive value of PAP for in-hospital death in patients with rheumatic mitral valve disease after valve replacement surgery. PAP>52.5mmHg had a sensitivity of 60.3% and specificity of 67.7% in predicting in-hospital death (AUC=0.672, 95%CI: 0.602-0.743, P<0.001, Figure 1). Kaplan-Meier analysis revealed that patients with PAP >52.5mmHg had higher one-year mortality than those without (Log-Rank=21.51, p<0.001) (Figure 2).

4. Discussion

This study found that pulmonary artery pressure (PAP) assessed by echocardiography can be a useful predictor for in-hospital death and one-year mortality after valve replacement surgery in patients with rheumatic mitral disease. In addition, 3.8% middle and aged patients receiving mitral valve replacement suffered death during or shortly after surgery which was in accordance with previous research. Furthermore, the cut-off of PAP>52.5mmHg can be suitable for risk assessment in middle and aged patients with rheumatic mitral disease.

Besides left to right bypass in congenital heart disease, RHD is another major cause for pulmonary hypertension (PH) due to the increased cardiac preload and passively chronic reconstruction of pulmonary vessels. [14] The chronic vessel remodeling could result in increased media thickness, intimal hyperplasia, fibrosis and ultimate narrowing of pulmonary vessels. [15] At present, there is no well-defined and recognized classification of pulmonary vascular pathology secondary to rheumatic heart disease. Mubeen et al enrolled 24 patients in a previous study who were diagnosed with RHD and pulmonary hypertension. The inferior lobe of right lung tissues was obtained during surgery and authors reported that the pathological changes of PH patients with RHD can be reversible. [16] Nevertheless, the study carried out by Tandon et al in about 100 patients with both RHD and pulmonary hypertension showed pathological change of telangiectasis, fibrous tissue proliferation and thickening, vessel stenosis and occlusion under the microscopy. More importantly, authors claimed that such pathologic changes were irreversible be reversible. [17]

Therefore, the conflicting results indicated that the degree of pathological changes and reconstruction of pulmonary vessels is closely related to the severity of PH.

RHD combined with pulmonary hypertension induced pathological changes of pulmonary vessels, since the progression of PH usually leads to the increased right cardiac afterload and later right ventricular hypertrophy (RVH) and heart failure. In the current study, we found that both RV diameter and NYHA were significantly different among different groups of PAP levels, with patients with highest PAP levels having the biggest RV diameter and highest percentage of NYHA>II, supporting the fact that a RV structure change has happened at a stage of severe PH. Moreover, severe pulmonary venous pleonaemia could lead to anoxia and carbon dioxide retention, which could further increase the heart damage, counting for a continuous deteriorating heart function. [18]

Although the stress of pulmonary artery and resistance of pulmonary vessels could be greatly decreased after rheumatic mitral regurgitation surgery, it is still not that common that pulmonary pressure of patients with RHD combined with severe pulmonary hypertension is able to return to normal level. In fact, due to the severe pulmonary vascular wall remodeling, the morphological change of pulmonary vessel wall is irreversible at later stage when patients receiving surgery and the pulmonary artery stress could persist and exceed the systemic arterial blood pressure before operation, the right cardiac afterload would be further aggravated after operation which may lead to low cardiac output syndrome. [19,20]

Pulmonary venous pleonaemia, pulmonary vascular remodeling and the decrease of lung compliance may increase the complication of patients with rheumatic mitral regurgitation combined severe pulmonary hypertension, leading to severe complications including respiratory failure. In addition, as the severity of pulmonary hypertension increases and vascular remodels, factors such as acute lung injury, anoxia or sympathetic stage in cardiopulmonary bypass in operation may also increase the possibility of complications, especially the pulmonary hypertensive crisis which has a more than 40% mortality. [21] The finding of our study proved that the more severe the pre-operative PAP level was, the higher in-hospital mortality and one-year follow-up mortality would be in patients with rheumatic mitral disease.

The significance of this study lies in the fact that we have a one-year follow up data sets. These data indicated that severe pulmonary hypertension may be a powerful predictor in the outcome of in-hospital death and one-year mortality after valve replacement surgery. To our best knowledge, this is the first study designed to focus on the value of PAP in deciding the prognosis of middle and aged patients with rheumatic mitral disease. In fact, PAP>52.5 mmHg had a sensitivity of 60.3% and specificity of 67.7% for predicting in-hospital death which was good enough as a preliminary result from a single center study. Moreover, it is possible that pulmonary hypertension may be a potential therapeutic target in valve replacement surgery of RHD although further studies are warranted to test this hypothesis.

There is limitation of the current study. Since the reproducibility and reliability of echocardiography in calculating PAP are lower than right-side heart catheterization,

[22] and we did not use invasive methods to measure PAP, this served as a major limitation of this study in establishing a clear correlation between PAP level and post-surgery mortality.

5. Conclusion

In conclusion, we found that PAP could serve as a predictor of postoperative in-hospital and one-year mortality after valve replacement surgery in patient with rheumatic mitral disease.

6. Competing Interests: None

7. Funding: None

8. Data sharing statement: No additional data are available.

9. **Contributors:** Dan-qing Yu and Ning Tan were contributed to conception or design. Lei Jiang, Xue-biao Wei, Peng-cheng He, Du Feng, Yuan-hui Liu and Jin Liu were contributed to collection and assembly of data. Xue-biao Wei and Peng-cheng He were contributed to data analysis and interpretation. Lei Jiang and Xue-biao Wei were contributed to manuscript writing. Dan-qing Yu, Ning Tan and Ji-yan Chen critically revised the manuscript. All authors were involved in final approval of the version to be published.

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357 Table 1：Clinical characteristics of the patients.

Clinical variables s	group A(n=268)	group B(n=771)	group C(n=384)	group D(n=216)	P
Age (year)	57.5±5.4	57.6±5.5	57.5±5.6	*57.0*±6.2	*0.594*
Females, n (%)	174(64.9)	532(69.0)	280(72.9)	*141(65.3)*	*0.104*
Smoking, n (%)	38(14.2)	82(10.6)	38(9.9)	21(9.7)	0.293
Hypertension, n (%)	33(12.3)	97(12.6)	39(10.2)	23(10.6)	0.617
Diabetes mellitus, n (%)	14(5.2)	43(5.6)	24(6.3)	20(9.3)	0.217
Coronary artery disease, n (%)	18(6.7)	45(5.8)	16(4.2)	10(4.6)	0.462
Atrial Fibrillation, n (%)	146(54.5)	504(65.4)	252(65.6)	128(59.3)	0.006
NYHA>II, n (%)	109(40.7)	316(41.0)	189(49.2)	125(57.9)	<0.001
GFR(mL/min/1.73 m^2)	89.6±26.4	88.0±24.3	88.0±26.1	*84.2*±24.5	*0.116*
hemoglobin	137.5±14.0	135.4±15.9	131.3±16.8	130.6±15.8	<0.001
LVEF	61.7±9.7	62.1±8.4	60.1±9.6	*62.1*±10.2	*0.004*
RV diameter, mm	48.9±7.7	50.2±6.8	53.7±7.6	*55.5*±9.0	*<0.001*
LVEDD index, mm/m²	50.5±9.8	49.0±7.9	49.0±8.6	*45.4*±9.2	*<0.001*
MR volume, mL	5.3(2.3,9.2)	5.8(2.5,10.1)	6.3(2.1,11.1)	*4.7(1.0,10.6)*	*0.025*

TR volume, mL	1.9(0,3.2)	4.8(2.8,7.4)	8.3(5.3,11.4)	*10.4(6.9,14.3)*	*<0.001*
Mitral stenosis	228(85.1)	670(86.9)	323(84.1)	*194(89.8)*	*0.222*
Aortic valve replacement	107(39.9)	302(39.2)	152(39.6)	*83(38.4)*	*0.988*
CABG	17(6.3)	35(4.5)	14(3.6)	*10(4.6)*	*0.452*
In-hospital death	5(1.9)	18(2.3)	18(4.7)	*22(10.2)*	*<0.001*

NYHA, New York Heart Association;GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; RV, right ventricle; LVEDD, left ventricular end-diastolic diameter; MR, Mitral regurgitation;TR, Tricuspid regurgitation; CABG, coronary artery bypass grafting.

Table 2: Univariate analysis and multiple logistic regression analysis for in-hospital death.

	Univariate analysis		Multiple logistic regression		
Clinical variables	OR	P	OR	95% CI	P
Age (year)	1.09	<0.001	1.07	1.02,1.12	0.006
Females	0.73	0.233			
Smoking	1.02	0.961			
Hypertension	1.27	0.518			
Diabetes mellitus	3.08	0.002	2.50	1.16,5.38	0.019
Coronary artery disease	1.53	0.374			
Atrial Fibrillation	0.84	0.491			
NYNA>II	1.66	0.052			
anemia	2.90	0.001	1.89	0.93,3.85	0.080
GFR<60mL/min/1.73 m^2	2.57	0.003	1.64	0.82,3.27	0.159
Mitral stenosis	0.83	0.604			
LVEF<50%	2.40	0.007	2.09	1.05,4.15	0.036
RV diameter	1.05	0.002	1.02	0.98,1.05	0.411

LVEDD index	1.02	0.196			
MR volume	1.01	0.801			
TR volume	1.07	<0.001	1.05	1.01,1.09	0.021
Aortic valve replacement	1.52	0.100			
CABG	3.23	0.003	2.96	1.26,6.93	0.012
PAP>70	3.82	<0.001	2.93	1.61,5.32	<0.001

NYHA, New York Heart Association;GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; RV, right ventricle; LVEDD, left ventricular end-diastolic diameter; MR, Mitral regurgitation;TR, Tricuspid regurgitation; CABG, coronary artery bypass grafting.

Figure legends

Figure 1: ROC curve of all patients in this study

Figure 2: Kaplan-Meier survival curve of different groups.

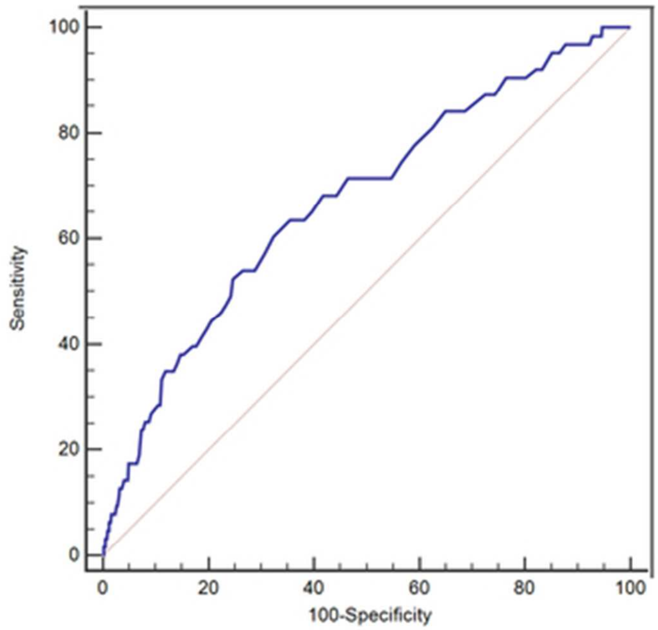

Figure 1: ROC curve of all patients in this study

19x14mm (600 x 600 DPI)

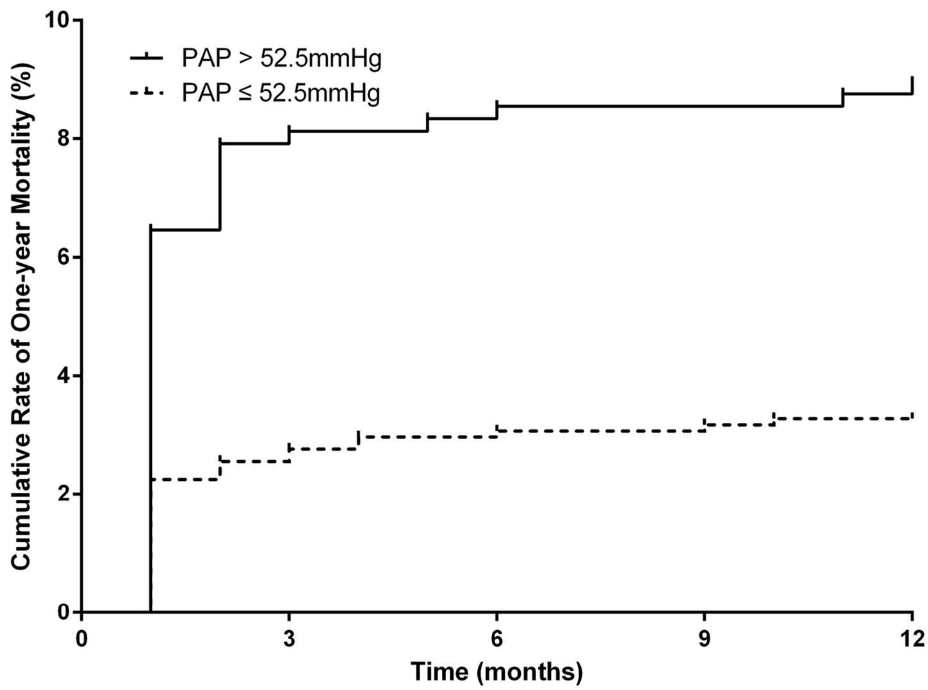

Figure 2: Kaplan-Meier survival curve of different groups

120x88mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract **In the title**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Done**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Done**
Objectives	3	State specific objectives, including any prespecified hypotheses **Done**
Methods		
Study design	4	Present key elements of study design early in the paper **Done**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Done**
Participants	6	(a) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Done** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **Done** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Done**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Done**
Bias	9	Describe any efforts to address potential sources of bias **Done**
Study size	10	Explain how the study size was arrived at **Done**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Done**

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding **Done**
		(*b*) Describe any methods used to examine subgroups and interactions **None**
		(*c*) Explain how missing data were addressed **None**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **None** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **Multiple logistic regression analysis**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Done**
		(b) Give reasons for non-participation at each stage **None**
		(c) Consider use of a flow diagram **None**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Done**
		(b) Indicate number of participants with missing data for each variable of interest **None**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Done**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Done**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Done**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **None**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Done**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Done**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Done**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Done**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **None**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Value of pulmonary artery pressure in predicting in-hospital death and one-year mortality after valve replacement surgery in middle and aged patients with rheumatic mitral disease: an observational study

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Value of pulmonary artery pressure in predicting in-hospital death and one-year mortality after valve replacement surgery in middle and aged patients with rheumatic mitral disease: an observational study

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Abstract

Objectives: To investigate the role of pulmonary artery pressure (PAP) in predicting in-hospital death after valve replacement surgery in middle and aged patients with rheumatic mitral disease.

Design: A observational study.

Setting: Guangdong General Hospital in China

Participants:1639 middle and aged patients (mean age 57±6 years) diagnosed with rheumatic mitral disease undergoing valve replacement surgery and receiving coronary angiography and transthoracic echocardiography before operation were enrolled.

Interventions: All participants underwent valve replacement surgery and received coronary angiography before operation.

Primary and secondary outcome measures: In-hospital death and one-year mortality after operation.

Methods: Included patients were divided into four groups based on the preoperative PAP obtained by echocardiogram: group A ($PAP \leq 30mmHg$); group B ($30mmHg < PAP \leq 50mmHg$), group C ($50mmHg < PAP \leq 70mmHg$) and group D ($PAP > 70mmHg$). The relationship between PAP and in-hospital death and cumulative rate of one-year mortality were evaluated.

Results: In-hospital mortality rate increased gradually but significantly as PAP level increased, with 1.9% in group A (n=268), 2.3% in group B (n=771), 4.7% in group C (n=384), and 10.2% in group D (n=216) ($P < 0.001$). Multivariate analysis showed that

PAP>70mmHg was an independent predictor of in-hospital death (OR=2.93, 95%CI: 1.61-5.32, P<0.001). PAP>52.5mmHg had a sensitivity of 60.3% and specificity of 67.7% in predicting in-hospital death (AUC=0.672, 95%CI: 0.602-0.743, P<0.001). Kaplan-Meier analysis showed that patients with PAP >52.5mmHg had higher one-year mortality after operation than those without (Log-Rank=21.51, p<0.001).

Conclusions: PAP could serve as a predictor of postoperative in-hospital and one-year mortality after valve replacement surgery in middle and aged patient with rheumatic mitral disease.

Key words: Pulmonary artery pressure, rheumatic mitral disease, valve replacement surgery, death

Strengths and limitations of this study

1.3.8% middle and aged patients receiving mitral valve replacement suffered death during or shortly after surgery

2.PAP could serve as a predictor of postoperative in-hospital mortality after valve replacement surgery in middle and aged patient with rheumatic mitral disease.

3.PAP>52.5mmHg had a sensitivity of 60.3% and specificity of 67.7% in predicting in-hospital death

4.PAP >52.5mmHg had higher one-year mortality after operation than those without.

5.Since the reproducibility and reliability of echocardiography in calculating PAP are lower than right-side heart catheterization, clear correlation between PAP level and post-surgery mortality was unknown.

1.Introduction

Rheumatic heart disease (RHD) caused by rheumatic fever has been uncommon in developed countries, but it still remains as a major health problem in developing countries. [1-3]

Approximately 50% of RHD affects mitral valve, resulting in mitral stenosis, mitral regurgitation, or both. [4] Valve replacement surgery is an important treatment for rheumatic mitral disease. [5] However, according to the meta-analysis conducted by Guida et al. [6], 2.95% (4293/145592) patients undergoing cardiac surgery including valve replacement suffered postoperative mortality. Therefore, identifying the high risk factor(s) for poor outcomes remains urgent and important.

Pulmonary hypertension (PH) is a common complication of rheumatic mitral disease which is correlated with poor outcome in patients undergoing heart surgery, particularly those middle and aged patients. [7] Pulmonary artery pressure (PAP) can be easily measured using Doppler echocardiography, which is currently considered the best screening method for PH. [8] However, whether the PAP could serve as a suitable readout or predictor for poor outcome particularly high mortality in patients with rheumatic mitral disease is not clearly and the cut-off value for PAP as a predictor has not been defined. The present study is designed to determine whether PAP measured by echocardiography could be a valuable parameter in predicting in-hospital death or cumulative rate of one-year mortality after surgery in middle and aged patients with rheumatic mitral disease.

2.Patients and Methods

2.1. Patients

In this study, we enrolled the middle and aged patients diagnosed as rheumatic mitral disease from Guangdong General Hospital, Guangzhou, China between March, 2009 and July, 2013. RHD was diagnosed according to previous acute rheumatic fever and/or symptom of precordial abnormalities, the presence of heart murmur, and the valve abnormality on echocardiography. [9] All patients received mitral valve replacement surgery in this study. PAP levels were measured using transthoracic echocardiography and coronary angiography was performed to exclude coronary heart disease in all patients. The exclusion criteria were (I) patients with known primary PH or pericardial disease, (II) patients presenting with pulmonary vessel disease and chronic obstructive pulmonary disease, (III) patients with previous valve replacement surgery and (IV) patients did not have echocardiographic examination before surgery.

1639 patients were divided into four groups based on the preoperative PAP on echocardiography. Patients in group A had PAP≤30mmHg (n=268); patients in group B had 30mmHg<PAP≤50mmHg (n=771); patients in group C had 50mmHg<PAP≤70mmHg (n=384) and patients in group D had PAP>70mmHg (n=216). The cut-off values were decided according to clinical guidelines (5,6). This study was approved by the Ethics Committee of the hospital (GDREC2014016H R1) and written informed consents were obtained from all enrolled participants.

2.2. Echocardiography

M-mode, 2-dimensional, and Doppler tissue imaging were performed according to guidelines of the American Society of Echocardiography [10] before valve replacement surgery. Left ventricular end-diastolic and Right ventricular diameter were obtained in the parasternal long-axis view by using M-mode images. Left ventricular ejection fraction (LVEF) was evaluated using the biplane Simpson's method. Mitral and tricuspid regurgitation were measured based on the jet area within the left or right atrium, respectively. Pulmonary artery pressure (PAP) was estimated by Doppler echocardiography with calculating the right ventricular to right atrial pressure gradient during systole, approximated by the modified Bernoulli equation as 4v2, where v is the velocity of the tricuspid regurgitation jet in m/s. [11] Although the agreement between echocardiographic estimates of PAP and invasively measured values on right-side heart catheterization is suboptimal, [12] especially among patients with lung disease, [13] echocardiography is a more convenient and practical approach than right-side heart catheterization. On the other hand, both echocardiography and right-side heart catheterization have been reported to be sufficient methodology PH screening. [14]

2.3. Definitions and endpoints

Coronary artery disease was defined as main coronary stenosis≥50 according to coronary angiography. The primary endpoint of this study was death from any cause except suicide during hospitalization. One-year mortality after operation was considered as secondary endpoint.

2.4. Statistical analysis

Continuous variables were described as mean± standard deviation (SD) and difference among groups was compared by analysis of variance (ANOVA) and post-hoc analysis was further performed to detect the difference between two particular groups. Abnormally distributed data was shown as median (first and third quartiles) and difference was analyzed by non-parametric Mann-Whitney U test. Categorical variables were shown in the format of numbers (percentages), and the comparison of the groups was done by $\chi2$ test. Multiple logistic regression analysis was performed to discovered the risk factors. Receive operative characteristic (ROC) was presented to evaluate the predictive value of PAP for in-hospital death. All the statistical analyses were carried out using SPSS 11.0 software program and $P < 0.05$ was considered statistically significant.

3.Results

3.1. Baseline clinical characteristics of the cohort

1749 middle and aged patients with rheumatic mitral valve disease underwent valve replacement surgery was originally enrolled in this study, among which 19 patients had a past medical history of valve replacement surgery. Preoperative echocardiography data was missing in 90 patients and 1 patient committed suicide during hospitalization, resulting in a final of 1639 patients being recruited in this study. 512 subjects were males and the remaining 1127 subjects were females with an average age of 57±6 years.

Other clinical characteristics of this population was summarized in Table 1. In brief, patients in other groups had higher incident of atrial fibrillation than patients in group A (p=0.006 of χ^2 test), possibly due to their high PAP and potentially changed left atrium structure. There were significant differences in the proportion of NYHA>II and right ventricle (RV) diameter among four groups, with patients in group D who had highest PAP having the largest percentage of subjects of NYHA>II and biggest RV diameter (Table 1). Lower hemoglobin was observed in group C and D compared with group A (ANOVA P<0.001, and post-hoc test P<0.05 vs group A). In addition, lower LVEDD index and mitral regurgitation volume were presented in group D (ANOVA P<0.001, and post-hoc test P<0.05 vs group A). Besides, patients in group C had a significantly lower LVEF compared with group A (p<0.05). Increasing PAP level was associated with higher tricuspid regurgitation volume (ANOVA P<0.001). 63 patients died during hospitalization with 5(1.9%) in group A, 18 (2.3%) in group B, 18 (4.7%) in group C and 22 (10.2%) in group D (p<0.001 of χ^2 test). No significant differences in the clinical data was observed among groups.

Among all these 1639 patients, 1459 subject (89.0%) completed the one-year follow-up after operation, during which time 75 patients died including 7(3.0%) in group A, 23 (3.3%) in group B, 20 (5.9%) in group C and 25(13.2%) in group D (p<0.001).

3.2. Correlation analysis between PAP levels and other parameters

Among all patients, PAP levels had positive correlation with RV diameter (r=0.270, p<0.001) and tricuspid regurgitation volume (r=0.507, p<0.001), and negative correlations with eGFR (r=−0.074 p=0.003), LVEDD index (r=−0.204, p<0.001) and hemoglobin concentrations (r=−0.141, p<0.001).

3.3. Role of PAP for in-hospital mortality

The univariate analyses for mortality showed that age, diabetes mellitus, anemia, lower eGFR, LVEF<50%, larger RV diameter, TR volume, previously received CABG and higher PAP were associated with increased in-hospital mortality (Table 2).Then we put these variables into multiple logistic regression analysis for adjustment of potential biased factor, we found that PAP>70mmHg (OR=2.93, 95%CI,1.61-5.32, P<0.001) remained an independent predictor of in-hospital death, after adjusting age, diabetes mellitus and previously received CABG. Of note, age (OR=1.07, 95%CI, 1.02,1.12, P=0.006), diabetes mellitus (OR=2.50, 95%CI, 1.16-5.38, P=0.019), LVEF<50% (OR=2.09, 95%CI, 1.05-4.15, P=0.036), TR volume (OR=1.05, 95%CI, 1.01-1.09, P=0.021) and received CABG (OR=2.96, 95%CI, 1.26-6.93, P=0.012) were also independent risk factors for in-hospital death (Table 2).

In addition, we performed a ROC curve to determine the predictive value of PAP for in-hospital death in patients with rheumatic mitral valve disease after valve replacement surgery. PAP>52.5mmHg had a sensitivity of 60.3% and specificity of 67.7% in predicting in-hospital death (AUC=0.672, 95%CI: 0.602-0.743, P<0.001, Figure 1). Kaplan-Meier analysis revealed that patients with PAP >52.5mmHg had higher one-year mortality than those without (Log-Rank=21.51, p<0.001) (Figure 2).

4. Discussion

This study found that pulmonary artery pressure (PAP) assessed by echocardiography can be a useful predictor for in-hospital death and one-year mortality after valve replacement surgery in patients with rheumatic mitral disease. In addition, 3.8% middle and aged patients receiving mitral valve replacement suffered death during or shortly after surgery which was in accordance with previous research. Furthermore, the cut-off of PAP>52.5mmHg can be suitable for risk assessment in middle and aged patients with rheumatic mitral disease.

Besides left to right bypass in congenital heart disease, RHD is another major cause for pulmonary hypertension (PH) due to the increased cardiac preload and passively chronic reconstruction of pulmonary vessels. [15] The chronic vessel remodeling could result in increased media thickness, intimal hyperplasia, fibrosis and ultimate narrowing of pulmonary vessels. [16] At present, there is no well-defined and recognized classification of pulmonary vascular pathology secondary to rheumatic heart disease. Mubeen et al enrolled 24 patients in a previous study who were diagnosed with RHD and pulmonary hypertension. The inferior lobe of right lung tissues was obtained during surgery and authors reported that the pathological changes of PH patients with RHD can be reversible. [17] Nevertheless, the study carried out by Tandon et al in about 100 patients with both RHD and pulmonary hypertension showed pathological change of telangiectasis, fibrous tissue proliferation and thickening, vessel stenosis and occlusion under the microscopy. More importantly, authors claimed that such pathologic changes were irreversible be reversible. [18]

Therefore, the conflicting results indicated that the degree of pathological changes and reconstruction of pulmonary vessels is closely related to the severity of PH.

RHD combined with pulmonary hypertension induced pathological changes of pulmonary vessels, since the progression of PH usually leads to the increased right cardiac afterload and later right ventricular hypertrophy (RVH) and heart failure. In the current study, we found that both RV diameter and NYHA were significantly different among different groups of PAP levels, with patients with highest PAP levels having the biggest RV diameter and highest percentage of NYHA>II, supporting the fact that a RV structure change has happened at a stage of severe PH. Moreover, severe pulmonary venous pleonaemia could lead to anoxia and carbon dioxide retention, which could further increase the heart damage, counting for a continuous deteriorating heart function. [19] Previous study has proved that right ventricular dysfunction was associated with poor outcomes. [20]

Although the stress of pulmonary artery and resistance of pulmonary vessels could be greatly decreased after rheumatic mitral regurgitation surgery, it is still not that common that pulmonary pressure of patients with RHD combined with severe pulmonary hypertension is able to return to normal level. In fact, due to the severe pulmonary vascular wall remodeling, the morphological change of pulmonary vessel wall is irreversible at later stage when patients receiving surgery and the pulmonary artery stress could persist and exceed the systemic arterial blood pressure before operation, the right cardiac afterload would be further aggravated after operation which may lead to low cardiac output syndrome. [21,22] Therefore, the postoperative mortality was still high in patient with higher PAP.

Pulmonary venous pleonaemia, pulmonary vascular remodeling and the decrease of lung compliance may increase the complication of patients with rheumatic mitral regurgitation combined severe pulmonary hypertension, leading to severe complications including respiratory failure. In addition, as the severity of pulmonary hypertension increases and vascular remodels, factors such as acute lung injury, anoxia or sympathetic stage in cardiopulmonary bypass in operation may also increase the possibility of complications, especially the pulmonary hypertensive crisis which has a more than 40% mortality. [23] The finding of our study proved that the more severe the pre-operative PAP level was, the higher in-hospital mortality and one-year follow-up mortality would be in patients with rheumatic mitral disease.

The significance of this study lies in the fact that we have a one-year follow up data sets. These data indicated that severe pulmonary hypertension may be a powerful predictor in the outcome of in-hospital death and one-year mortality after valve replacement surgery. To our best knowledge, this is the first study designed to focus on the value of PAP in deciding the prognosis of middle and aged patients with rheumatic mitral disease. In fact, PAP>52.5 mmHg had a sensitivity of 60.3% and specificity of 67.7% for predicting in-hospital death which was good enough as a preliminary result from a single center study. Moreover, it is possible that pulmonary hypertension may be a potential therapeutic target in valve replacement surgery of RHD. A future randomized trial is warranted to confirm whether decreasing PAP by drugs [24,25] below the cut-off point indicated in our study would lead to a better outcome.

There were some limitations of the current study. First,as a retrospective analysis based on prospectively collected data, there were some possible confounding might affect the results. To overcome this inherent weakness, multivariate logistic regression was performed. Second, PAP was not measured by right-side heart catheterization, the gold standard, which was more reliability than echocardiography. [26] Even so, echocardiography is a more convenient and practical approach than right-side heart catheterization. Third, whether postoperative PAP affecting the prognosis was unclear because PAP could not be accurately measured by echocardiography in patients with tricuspid valve repair.

5. Conclusion

In conclusion, we found that PAP could serve as a predictor of postoperative in-hospital and one-year mortality after valve replacement surgery in middle and aged patient with rheumatic mitral disease.

6. Competing Interests: None

7. Funding: None

8. Data sharing statement: No additional data are available.

9. **Contributors:** Dan-qing Yu and Ning Tan were contributed to conception or design. Lei Jiang, Xue-biao Wei, Peng-cheng He, Du Feng, Yuan-hui Liu and Jin Liu were contributed to collection and assembly of data. Xue-biao Wei and Peng-cheng He

were contributed to data analysis and interpretation. Lei Jiang and Xue-biao Wei were contributed to manuscript writing. Dan-qing Yu, Ning Tan and Ji-yan Chen critically revised the manuscript. All authors were involved in final approval of the version to be published.

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Table 1：Clinical characteristics of the patients.

Clinical variables s	group A(n=268)	group B(n=771)	group C(n=384)	group D(n=216)	P
Age (year)	57.5±5.4	57.6±5.5	57.5±5.6	57.0±6.2	0.594
Females, n (%)	174(64.9)	532(69.0)	280(72.9)	141(65.3)	0.104
Smoking, n (%)	38(14.2)	82(10.6)	38(9.9)	21(9.7)	0.293
Hypertension, n (%)	33(12.3)	97(12.6)	39(10.2)	23(10.6)	0.617
Diabetes mellitus, n (%)	14(5.2)	43(5.6)	24(6.3)	20(9.3)	0.217
Coronary artery disease, n (%)	18(6.7)	45(5.8)	16(4.2)	10(4.6)	0.462
Atrial Fibrillation, n (%)	146(54.5)	504(65.4)	252(65.6)	128(59.3)	0.006
NYHA>II, n (%)	109(40.7)	316(41.0)	189(49.2)	125(57.9)	<0.001
eGFR(mL/min/1.73 m^2)	89.6±26.4	88.0±24.3	88.0±26.1	84.2±24.5	0.116
Hemoglobin (g/L)	137.5±14.0	135.4±15.9	131.3±16.8	130.6±15.8	<0.001
LVEF,%	61.7±9.7	62.1±8.4	60.1±9.6	62.1±10.2	0.004
RV diameter, mm	48.9±7.7	50.2±6.8	53.7±7.6	55.5±9.0	<0.001
LVEDD index, mm/m^2	50.5±9.8	49.0±7.9	49.0±8.6	45.4±9.2	<0.001
MR volume, cm2					

<4	107(29.9)	278(36.1)	147(38.3)	104(48.1)	0.003
4-8	73(27.2)	208(27.0)	82(21.4)	35(16.2)	
>8	88(32.8)	285(37.0)	155(40.4)	77(35.6)	
MVA ≤1.5 cm2	228(85.1)	670(86.9)	323(84.1)	194(89.8)	0.222
TR volume, cm2	1.9(0,3.2)	4.8(2.8,7.4)	8.3(5.3,11.4)	10.4(6.9,14.3)	<0.001
Aortic valve replacement	107(39.9)	302(39.2)	152(39.6)	83(38.4)	0.988
CABG	17(6.3)	35(4.5)	14(3.6)	10(4.6)	0.452
In-hospital death	5(1.9)	18(2.3)	18(4.7)	22(10.2)	<0.001

NYHA, New York Heart Association;GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; RV, right ventricle; LVEDD, left ventricular end-diastolic diameter; MR, Mitral regurgitation;TR, Tricuspid regurgitation; MVA, mitral valve area; CABG, coronary artery bypass grafting.

391 Table 2: Univariate analysis and multiple logistic regression analysis for in-hospital
392 death.

	Univariate analysis		Multiple logistic regression		
Clinical variables	OR	P	OR	95% CI	P
Age (year)	1.09	<0.001	1.07	1.02,1.12	0.006
Females	0.73	0.233			
Smoking	1.02	0.961			
Hypertension	1.27	0.518			
Diabetes mellitus	3.08	0.002	2.50	1.16,5.38	0.019
Coronary artery disease	1.53	0.374			
Atrial Fibrillation	0.84	0.491			
NYNA>II	1.66	0.052			
anemia	2.90	0.001	1.89	0.93,3.85	0.080
GFR<60mL/min/1.73 m^2	2.57	0.003	1.64	0.82,3.27	0.159
MVA ≤1.5 cm2	0.83	0.604			
LVEF<50%	2.40	0.007	2.09	1.05,4.15	0.036
RV diameter	1.05	0.002	1.02	0.98,1.05	0.411

LVEDD index	1.02	0.196			
MR>8cm^2	1.05	0.843			
TR volume	1.07	<0.001	1.05	1.01,1.09	0.021
Aortic valve replacement	1.52	0.100			
CABG	3.23	0.003	2.96	1.26,6.93	0.012
PAP>70mmHg	3.82	<0.001	2.93	1.61,5.32	<0.001

NYHA, New York Heart Association;GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; RV, right ventricle; LVEDD, left ventricular end-diastolic diameter; MR, Mitral regurgitation;TR, Tricuspid regurgitation; CABG, coronary artery bypass grafting.

Figure legends

Figure 1: ROC curve of all patients in this study

Figure 2: Kaplan-Meier survival curve of different groups.

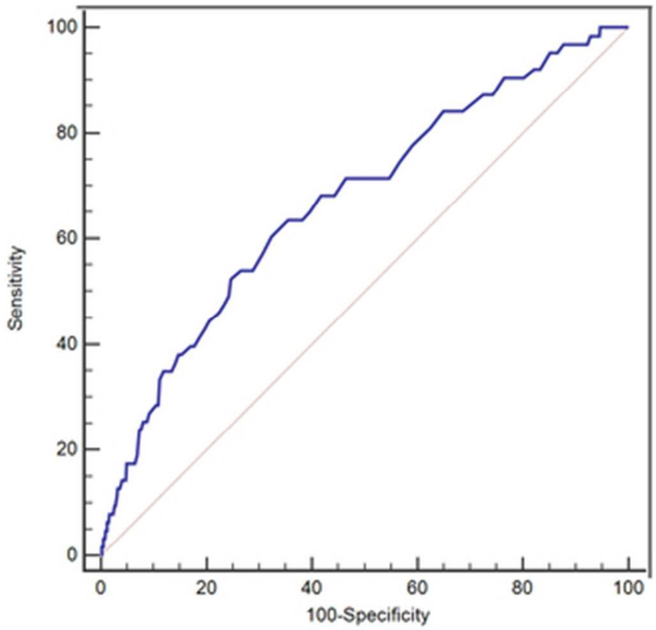

Figure 1: ROC curve of all patients in this study

19x14mm (600 x 600 DPI)

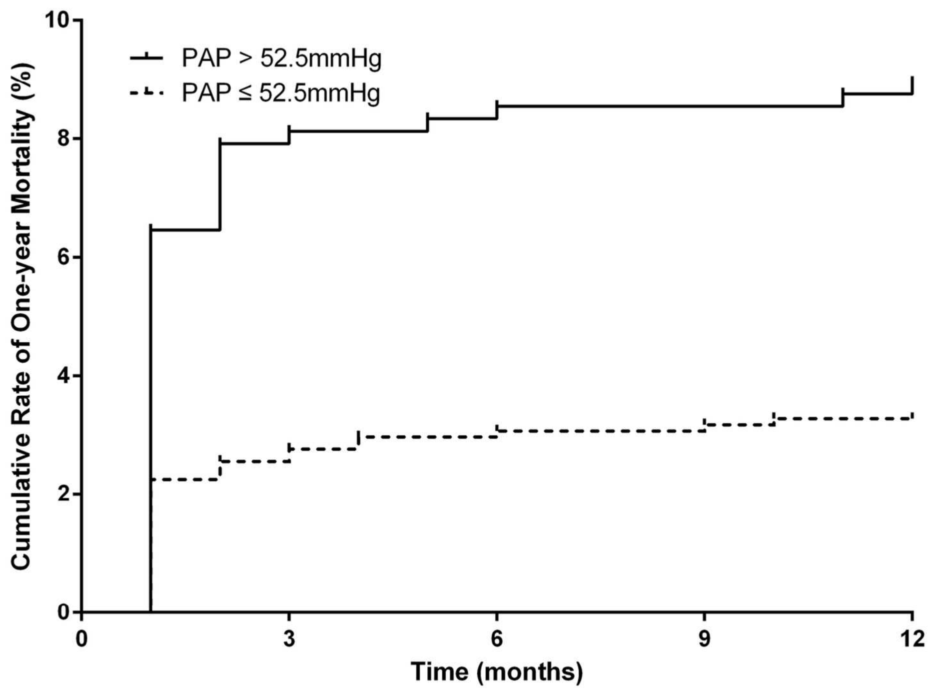

Figure 2: Kaplan-Meier survival curve of different groups

120x88mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract **In the title**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Done**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Done**
Objectives	3	State specific objectives, including any prespecified hypotheses **Done**
Methods		
Study design	4	Present key elements of study design early in the paper **Done**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Done**
Participants	6	(a) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Done** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **Done** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Done**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Done**
Bias	9	Describe any efforts to address potential sources of bias **Done**
Study size	10	Explain how the study size was arrived at **Done**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Done**

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding **Done**
		(*b*) Describe any methods used to examine subgroups and interactions **None**
		(*c*) Explain how missing data were addressed **None**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **None** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **Multiple logistic regression analysis**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Done**
		(b) Give reasons for non-participation at each stage **None**
		(c) Consider use of a flow diagram **None**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Done**
		(b) Indicate number of participants with missing data for each variable of interest **None**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Done**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Done**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Done**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **None**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Done**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Done**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Done**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Done**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **None**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.